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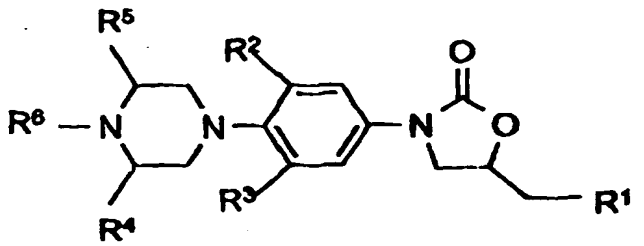
(54) Title: SUBSTITUTED PIPERAZINYL-PHENYL-OXAZOLIDINONE DERIVATIVES AND THEIR USE AS ANTI-BACTERIAL AGENTS

(57) Abstract



(I)

The invention concerns a compound of formula (I) wherein, for example: R^1 is of the formula -NHC(=O)R^a wherein R^a is for example (1-4C)alkyl; R^2 and R^3 are independently hydrogen or fluoro; R^4 and R^5 are independently hydrogen or methyl; R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, and optionally substituted by substituents selected from (1-4C)alkyl (optionally substituted), halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylS(O)$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl (optionally substituted by carboxy or (1-4C)alkoxycarbonyl), (1-4C)alkoxy, cyano or nitro; pharmaceutically-acceptable salts, suitable N-oxides and in-vivo-hydrolysable esters thereof; processes for their preparation; pharmaceutical compositions containing them and their use as antibacterial agents.

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SUBSTITUTED PIPERAZINYL-PHENYL-OXAZOLIDINONE DERIVATIVES AND THEIR USE AS ANTI-BACTERIAL AGENTS

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing an oxazolidinone ring. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded primarily as effective against Gram-positive pathogens because of their particularly good activity against such pathogens.

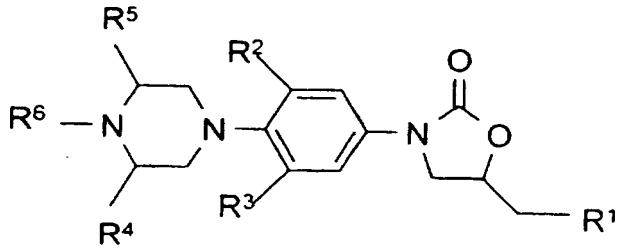
Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant streptococcus pneumoniae and multiply resistant Enterococcus faecium.

The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with nephrotoxicity and ototoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens.

The present inventors have discovered a class of antibiotic compounds containing an oxazolidinone ring which has useful activity against Gram-positive pathogens including MRSA and MRCNS and, in particular, against various strains exhibiting resistance to vancomycin and against E. faecium strains resistant to both aminoglycosides and clinically used β-lactams.

We have now discovered a range of compounds that have good activity against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics. In comparison with compounds described in the art (for example Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165) the compounds also possess a favourable toxicological profile.

Accordingly the present invention provides a compound of the formula (I)



(I)

wherein:

R^1 is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, or of the formula $-NHC(=O)R^a$ wherein R^a is hydrogen, (1-4C)alkoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl, methylamino, dimethylamino or (1-4C)alkyl or R^1 is of the formula $-N(Me)C(=O)R^b$ wherein R^b is hydrogen, methyl or methoxy or R^1 is of the formula $-NHS(O)_n$(1-4C)alkyl wherein n is 0, 1 or 2;

R^2 and R^3 are independently hydrogen or fluoro;

R^4 and R^5 are independently hydrogen or methyl;

R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl (optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino), halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2),

(1-4C)alkylS(O)$_n$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl (optionally substituted by carboxy or (1-4C)alkoxycarbonyl), (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; and suitable N-oxides thereof.

In this specification the term "alkyl" includes straight chained and branched structures. For example, (1-6C)alkyl includes propyl, isopropyl and tert-butyl. However, references to individual alkyl groups such as "propyl" are specific for the straight chained version only, and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only.

In this specification a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, includes pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine.

Examples of (1-4C)alkyl include methyl, ethyl, propyl, isopropyl and tert-butyl; examples of halo include fluoro, chloro, bromo and iodo; examples of N-(1-4C)alkylcarbamoyl include methylcarbamoyl, ethylcarbamoyl and propylcarbamoyl; examples of di-(N-(1-4C)alkyl)carbamoyl include di-(methyl)carbamoyl and di-(ethyl)carbamoyl; examples of the (1-4C)alkyl group or groups in N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl being optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl include 2-hydroxyethylaminocarbonyl, bis-(2-hydroxyethyl)aminocarbonyl, 2-methoxyethylaminocarbonyl and methoxycarbonylmethylaminocarbonyl; examples of (1-4C)alkylS(O)$_n$ include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of (1-4C)alkylS(O)$_n$amino include methylsulfonylamino and ethylsulfonylamino; examples of (2-4C)alkenyl include allyl and vinyl; examples of (1-4C)alkoxy include methoxy, ethoxy and propoxy; examples of (1-4C)alkanoylamino include formamido, acetamido and propionylamino; examples of (2-4C)alkanoylamino include acetamido and propionylamino; examples of N-(1-4C)alkylamino include methylamino and ethylamino; examples of di-(N-(1-

4C)alkyl)amino include di-N-methylamino, di-(N-ethyl)amino and N-ethyl-N-methylamino; examples of (1-4C)alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, n- and tert-butoxycarbonyl ; examples of (1-4C)alkanesulfonyloxy include methanesulfonyloxy and ethanesulfonyloxy; and examples of (1-4C)alkylaminocarbonyloxy include methylaminocarbonyloxy and ethylaminocarbonyloxy.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

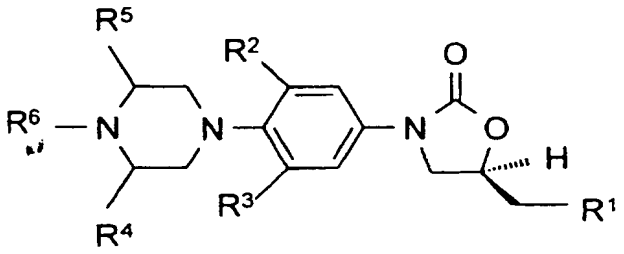
In this specification a suitable N-oxide refers to the N-oxides which may be formed on an available nitrogen atom in either the piperazine ring or in the heteroaryl ring R^6. A suitable N-oxide may be optionally in the form of a pharmaceutically-acceptable salt.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the formula (I).

An in-vivo hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An in-vivo hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino or piperazino linked from a ring nitrogen atom via methylamino to the 3- or 4-position of the benzoyl ring.

The compounds of the present invention have a chiral centre at the C-5 position of the oxazolidinone ring. The pharmaceutically active enantiomer is of the formula (IA):



(IA)

The present invention includes the pure enantiomer depicted above or mixtures of the 5R and 5S enantiomers, for example a racemic mixture. If a mixture of enantiomers is used, a larger amount (depending upon the ratio of the enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer. For the avoidance of doubt the enantiomer depicted above could be either 5R or 5S depending upon the value of R^1. For example, when R^1 is acetamido, the enantiomer depicted above is the 5S enantiomer and when R^1 is hydroxy, the enantiomer depicted above is the 5R enantiomer.

Furthermore, some compounds of the formula (I) may have other chiral centres. It is to be understood that the invention encompasses all such optical and diastereo-isomers that possess antibacterial activity.

The invention relates to all tautomeric forms of the compounds of the formula (I) that possess antibacterial activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial activity.

In a further aspect of the invention there is provided a compound of the formula (I) wherein:

R^1 is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, or R^1 is of the formula $-NHC(=O)R^a$ wherein R^a is hydrogen, (1-4C)alkoxy, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl or R^1 is of the formula $-NHSO_2$(1-4C)alkyl

R^2 and R^3 are independently hydrogen or fluoro;

R^4 and R^5 are independently hydrogen or methyl;

R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino], halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl [optionally substituted by carboxy or (1-4C)alkoxycarbonyl], (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof: and suitable N-oxides thereof.

In another further aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt thereof, as defined in the above aspects of the invention, except that suitable N-oxides are excluded.

In a yet further aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof, as defined anywhere above, except that the following optional substituents on R^6, namely (1-4C)alkoxy, (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino and those N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl substituents with the (1-4C)alkyl group or groups substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl, are excluded: and the number of optional substituents on R^6 is restricted to one or two. For the avoidance of doubt, in the preceding yet further aspect of the invention suitable N-oxides are optionally excluded.

In a preferred aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof, wherein the substituents R^1 to R^6 and other optional substituents mentioned above have the values disclosed hereinbefore, or any of the following values :

(a) Preferably R^1 is hydroxy, chloro, fluoro, methanesulfonyloxy, amino, azido, methoxy, methylthio, methylaminocarbonyloxy, or of the formula -NHC(=O)R^a wherein R^a is hydrogen, methoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl, methylamino, dimethylamino or (1-4C)alkyl or R^1 is of the formula -N(Me)C(=O)R^b wherein R^b is hydrogen, methyl or methoxy or R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2.

(b) More preferably R^1 is hydroxy, chloro, fluoro, methanesulfonyloxy, or of the formula -NHC(=O)R^a wherein R^a is hydrogen, methoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl or R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2.

(c) Yet more preferably R^1 is hydroxy, or of the formula -NHC(=O)R^a wherein R^a is (1-4C)alkyl or R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2.

(d) When R^1 is of the formula -NHS(O)$_n$(1-4C)alkyl wherein n is 0, 1 or 2, n is preferably 2.

(e) Yet more preferably R^1 is of the formula -NHC(=O)(1-4C)alkyl.

(f) Most preferably R^1 is acetamido.

(g) In another aspect R^1 is hydroxy.

(h) Preferably one of R^2 and R^3 is hydrogen and the other is fluoro.

(i) Preferably at least one of R^4 and R^5 is hydrogen.

(j) Preferably R^4 and R^5 are both hydrogen.

(k) Preferably the heteroaryl ring in R^6 is pyrimidine, pyridazine or pyrazine.

(l) Yet more preferably the heteroaryl ring in R^6 is pyrimidine or pyrazine.

(m) Still more preferably the heteroaryl ring in R^6 is pyrimidin-2-yl or pyrazin-2-yl.

(n) Most preferably the heteroaryl ring in R^6 is pyrimidin-2-yl.

(o) Preferably optional substituents on the heteroaryl ring are not positioned in the 2-position relative to the ring carbon atom which is attached to the piperazine ring.

(p) Preferably the optional substituents on the heteroaryl ring are independently selected from (1-4C)alkyl (optionally substituted by (1-4C)alkoxy or (2-4C)alkanoylamino), (1-4C)alkylthio, halo, carboxy, (1-4C)alkoxycarbonyl, and carbamoyl.

(q) More preferably the optional substituents on the heteroaryl ring are independently selected from methyl or ethyl (each optionally substituted by methoxy, ethoxy or acetamido), methylthio, ethylthio, chloro, bromo, carboxy, methoxycarbonyl, ethoxycarbonyl and carbamoyl.

(r) Yet more preferably the optional substituents on the heteroaryl ring are independently selected from methyl, ethyl, methoxymethyl, 2-(acetamido)ethyl, methylthio, chloro, bromo, carboxy, methoxycarbonyl and carbamoyl.

(s) Most preferably the optional substituents on the heteroaryl ring are independently selected from (1-4C)alkyl (preferably methyl), halo (preferably chloro), nitro, cyano, carbamoyl, N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl.

(t) Preferably the heteroaryl ring is unsubstituted or substituted by one substituent.

(u) Most preferably the heteroaryl ring is unsubstituted.

Therefore, especially preferred compounds of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof, are those defined above wherein

R^1 is acetamido, one of R^2 and R^3 is hydrogen and the other is fluoro, R^4 and R^5 are both hydrogen, R^6 is pyrimidine or pyrazine and the optional substituents on the heteroaryl ring are independently selected from methyl, chloro, nitro, cyano, carbamoyl, N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl.

Particular compounds of the present invention include :

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-nitropyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(4-amino-5-cyanopyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(4-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

N-[(5S)-3-(4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

N-[(5S)-3-(4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

Further particular compounds of the present invention include :

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(3-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

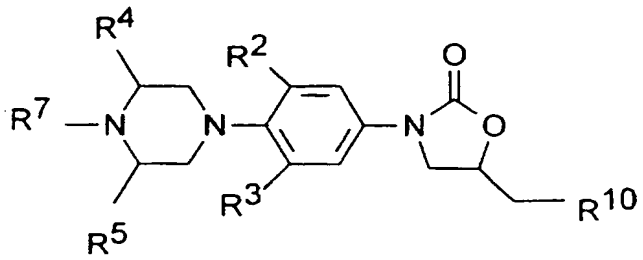
Especially preferred compounds of the invention include

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide;

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

In a further aspect the present invention provides a process for preparing a compound of the formula (I), a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof. The compounds of the formula (I), a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof may be prepared by deprotecting a compound, containing at least one protecting group, of the formula (II), a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof :



(II)

wherein R^2, R^3, R^4 and R^5 are as hereinabove defined. R^7 is R^6 or protected R^6 and R^{10} is R^1 or protected R^1 and thereafter if necessary forming a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (eg isopropyl, tert-butyl); lower alkoxy lower alkyl groups (eg methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (eg acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (eg 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (eg p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (eg trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (eg trimethylsilylethyl); and (2-6C)alkenyl groups (eg allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include lower alkenyl groups (eg allyl); lower alkanoyl groups (eg acetyl); lower alkoxycarbonyl groups (eg tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (eg trimethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl); aryl lower alkyl groups (eg benzyl) groups; and triaryl lower alkyl groups (eg triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (eg benzyl and substituted benzyl, eg p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (eg tert-butoxycarbonyl); lower alkenyloxycarbonyl (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (eg trimethylsilyl and tert-butyldimethylsilyl); alkylidene (eg methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, metal- or enzymically-catalysed hydrolysis, for groups such as o-nitrobenzyloxycarbonyl, photolytically and for groups such as silyl groups, fluoride.

Examples of protecting groups for amide groups include aralkoxymethyl (eg. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (eg. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (eg. trimethylsilyl, tert-butyldimethylsilyl,

by reacting the amide with the appropriate chloride and removing with acid, or in the case of the silyl containing groups fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

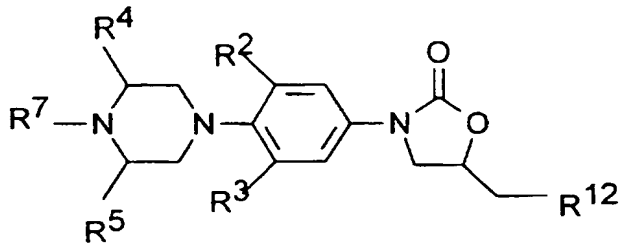
For further examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons).

In another aspect of the present invention the compounds of the formulae (I) and (II), pharmaceutically-acceptable salts, suitable N-oxides and in-vivo hydrolysable esters thereof can be prepared:

(a) by modifying a substituent in or introducing a substituent into another compound of formula (I) or (II);

(b) when R^1 or R^{10} is of the formula - $NHS(O)_n$(1-4C)alkyl, wherein n is 1 or 2, by oxidising a compound of the formula (I) wherein n is 0 or, when n is 2 by oxidising a compound of the formula (I) or (II) wherein n is 1;

(c) when R^1 or R^{10} is azido, by reacting a compound of the formula (III) with a source of azide:



(III)

(d) when R^1 or R^{10} is amino, by reducing a compound of the formula (I) or (II) wherein R^1 or R^{10} is azido;

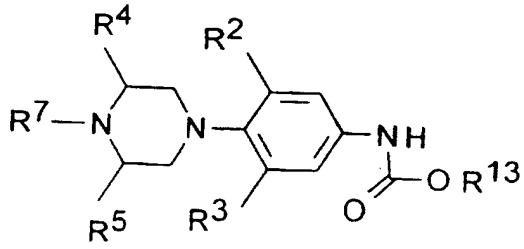
(e) when R^1 or R^{10} is of the formula -NHC(=O)R^a, by introducing -C(=O)R^a into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

(f) when R^1 or R^{10} is of the formula -$NHS(O)_n$ (1-4C)alkyl by introducing -$S(O)_n$ (1-4C)alkyl into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

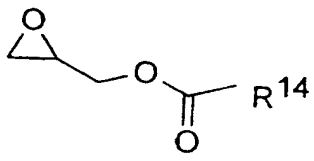
(g) when R^1 or R^{10} is chloro, fluoro, (1-4C)alkanesulfonyloxy or (1-4C)alkylaminocarbonyloxy, from a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy;

(h) when R^1 or R^{10} is chloro, (1-4C)alkylthio or (1-4C)alkoxy, from a compound of the formula (III);

(i) when R^1 or R^{10} is hydroxy, by reacting a compound of the formula (IV) with a compound of the formula (V):

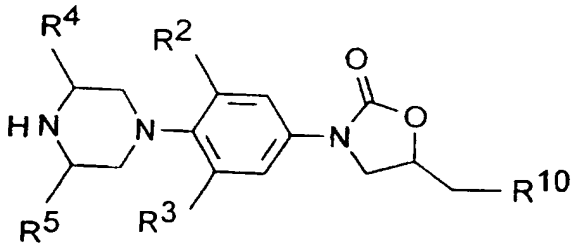


(IV)



(V)

(j) by reacting a compound of the formula (VI) with a compound of the formula (VII):



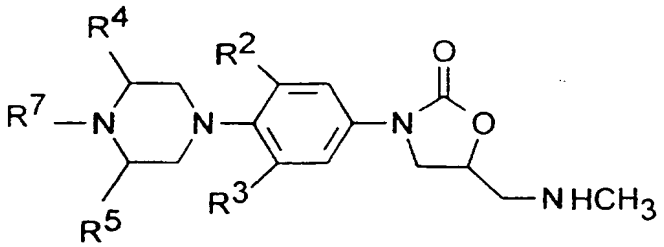
(VI)

R^7-L^1

(VII)

(k) when R^{10} is of the formula -N(CO_2R^{15})CO(1-4C)alkyl; from a compound of the formula (I) and (II) wherein R^1 or R^{10} is hydroxy;

(l) when R^1 or R^{10} is of the formula -N(Me)C(=O)R^b, by introducing the group -C(=O)R^b into a compound of the formula (VIII):



(VIII)

and

(m) when a suitable N-oxide is required, by preparation directly from a corresponding parent compound of the formula (I) or (II), or by assembly from suitable N-oxide starting materials;

wherein R^2 - R^5 and R^7 and R^{10} are as hereinabove defined. R^{12} is mesyloxy or tosyloxy, R^{13} is (1-6C)alkyl or benzyl. R^{14} is (1-6C)alkyl. R^{15} is (1-4C)alkyl or benzyl and L^1 is a leaving goup and thereafter if necessary:

i) removing any protecting groups;

ii) forming a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester.

Methods for converting substituents into other substituents are known in the art. For example, an alkylthio group may be oxidised to an alkylsulfinyl or alkysulfonyl group, a cyano group reduced to an amino group, a nitro group reduced to an amino group, an amino group converted to an acetamido or sulfonamido group, a hydroxy group alkylated to a methoxy group, a carboxy group converted to a carbamoyl group, an N-(1-4C)alkylcarbamoyl or di-(N-(1-4C)alkyl)carbamoyl group, or a bromo group converted to an alkylthio group. Also for example, a chloro group may be introduced at an unsubstituted position in R^7, or a chloro group may be removed from R^7 (by, for example, hydrogenation as in Examples 9 and 31).

Compounds of the formula (I) or (II) wherein R^1 or R^{10} is $-NHS(O)_n$(1-4C)alkyl can be prepared by oxidising a compound of the formula (I) or (II) with standard reagents known in the art for the oxidation of a thio group to a sulfinyl or sulfonyl group. For example, a thio group may be oxidised to a sulfinyl group with a peracid such as m-chloroperoxybenzoic acid and oxidising agents such as potassium permanganate will

convert a thio group to a sulfonyl group. Compounds of the formula (I) or (II) wherein R^1 or R^{10} is -NHS(1-4C)alkyl can be prepared by reacting compounds of the formula (I) or (II) wherein R^1 or R^{10} is amino with a reagent such as (1-4C)alkylSCl.

A compound of the formula (I) or (II) wherein R^1 or R^{10} is azido may be prepared, for example, by reacting a compound of the formula (III) with sodium azide in an inert solvent such as DMF in a temperature range of ambient to 100°C, normally in the region of 75°C - 85°C. A compound of the formula (III) may be prepared by converting the hydroxy group in a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy into a tosyloxy or mesyloxy group by standard methods known in the art. For example, by reacting the compound of the formula (I) or (II) with tosyl chloride or mesyl chloride in the presence of a mild base such as triethylamine, or pyridine.

Suitable reducing agents for reducing azido to amino in a compound of the formula (I) or (II) include triethylamine/hydrogen sulfide, triphenylphosphine or phosphite ester, or hydrogen in the presence of a catalyst. More specifically the reduction of the azido group may be carried out by heating it in an aprotic solvent, such as 1,2-dimethoxyethane, in the presence of $P(OMe)_3$ and subsequently heating in 6N aqueous hydrochloric acid, or reacting it with hydrogen in the presence of palladium on carbon in a solvent such as DMF or ethyl acetate. For further details on the reduction of azides to amines see USP 4,705,799. The azido compound may be reduced and converted to a compound of the formula (I) or (II), wherein R^1 or R^{10} is acetamido, in situ using acetic anhydride in DMF.

When R^a is (1-4C)alkyl, the group -C(=O)(1-4C)alkyl may be introduced into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino by standard acetylation procedures. For example, the amino group may be acetylated to give an acetamido group using the Schotten-Baumann procedure i.e. reacting the compound of the formula (I) or (II) wherein R^1 or R^{10} is amino with acetic anhydride in aqueous sodium hydroxide and THF in a temperature range of 0°C to ambient temperature. Preferably the acylation is carried out in situ following the catalytic hydrogenation of a compound of the formula (I) or (II) wherein R^1 or R^{10} is azido, by performing the hydrogenation in the presence of acetic anhydride (for example using similar methods to those used in Example 15).

When R^a is hydrogen, the -CHO group may be introduced into the compound of the formula (I) or (II) wherein R^1 or R^{10} is amino (amino compound) by reacting the latter

compound with formic acetic anhydride, in an inert organic solvent such as THF, in a temperature range of 0°C to ambient temperature, or by reacting it with ethyl formate in an inert organic solvent in the temperature range of 50-100°C.

When R^a is (1-4C)alkoxy, the -COO(1-4C)alkyl group may be introduced into the amino compound by reacting the latter compound with (1-4C)alkyl chloroformate, in the presence of an organic base such as triethylamine, in an organic solvent such as dichloromethane and in a temperature range of 0°C to ambient temperature.

When R^a is amino, the $-CONH_2$ group may be introduced into the amino compound by reacting the latter compound either with potassium cyanate in aqueous acid (eg hydrochloric acid) in a temperature range of ambient temperature to 40°C or with phenyl carbamate in glyme at reflux.

When R^a is chloromethyl, dichloromethyl, cyanomethyl or methoxymethyl, the $-C(=O)R^a$ group may be introduced into the amino compound by reacting the latter compound with the appropriate acid chloride under standard conditions. The acid chloride may be prepared from the appropriate acid. When R^a is acetylmethyl, the $-C(=O)R^a$ group may be introduced into the amino compound by reacting the latter compound with diketene, in an inert organic solvent such as THF, in a temperature range of 0°C to ambient temperature.

Alternatively, the amino compound may be reacted with the appropriate acid anhydride, in dichloromethane or THF, in the presence of an organic base such as triethylamine and in a temperature range of 0°C to ambient temperature, or the amino compound may be reacted with the appropriate acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and an organic base such as triethylamine, in an organic solvent such as dichloromethane, in a temperature range of 0°C to ambient temperature.

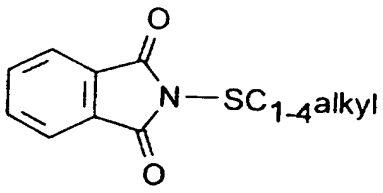
When R^a is methylamino, the -CONHMe group may be introduced into the amino compound by reacting the latter compound with methyl isocyanate in an organic solvent such as THF or acetonitrile, in a temperature range of 0°C to ambient temperature.

When R^a is dimethylamino, the $-CONMe_2$ group may be introduced into the amino compound my reacting the latter compound with dimethylcarbamoyl chloride and triethylamine in an organic solvent such as THF or acetonitrile, in a temperature range of 0°C to ambient temperature.

Standard reaction conditions for the conversion of a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino to a compound of the formula (I) or (II) wherein R^1 or R^{10} is sulfonamido are known in the art. For example, a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino could for example be converted to a compound of the formula (I) or (II) wherein R^1 or R^{10} is (1-4C)alkylSO_2NH- by reacting the former compound with a sulfonyl chloride, for example, mesyl chloride, in a mild base such as pyridine.

Alternatively compounds of the formula (I) or (II) wherein R^1 or R^{10} is (1-4C)alkylSO_2NH- or (1-4C)alkylSONH- may be prepared by reacting a compound of the formula (I) or (II) wherein R^1 is amino with a compound of the formula (1-4C)alkylSO_2L^2 or (1-4C)SOL^2 wherein L^2 is a phthalimido group.

The phthalimido compound may be prepared by oxidising a compound of the formula (IX):



(IX)

with standard oxidising agents known for the conversion of a thio group to a sulfinyl or sulfonyl group.

Compounds of the formula (IX) can be prepared by reacting phthalimide with an alkylthiochloride ((1-4C)alkylSCl).

A compound of the formula (I) or (II) wherein R^1 or R^{10} is fluoro may be prepared by reacting a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy (hydroxy compound) with a fluorinating agent such as diethylaminosulfur trifluoride in an organic solvent such as dichloromethane in the temperature range of 0°C to ambient temperature.

When R^1 or R^{10} is chloro, the compound of the formula (I) or (II) may be formed by reacting the hydroxy compound with a chlorinating agent. For example, by reacting the hydroxy compound with thionyl chloride in a temperature range of ambient temperature to reflux, optionally in a chlorinated solvent such as dichloromethane or by reacting the hydroxy compound with carbon tetrachloride/triphenyl phosphine in dichloromethane, in a temperature range of 0°C to ambient temperature.

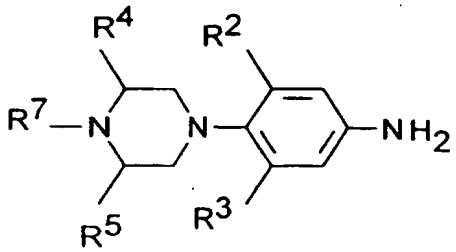
The (1-4C)alkanesulfonyloxy compound may be prepared by reacting the hydroxy compound with (1-4C)alkanesulfonyl chloride in the presence of a mild base such as triethylamine or pyridine.

The (1-4C)alkylaminocarbonyloxy compound may be prepared by reacting the hydroxy compound with (1-4C)alkyl cyanate in an organic solvent such as THF or acetonitrile, in the presence of triethylamine, in a temperature range of 0°C to 50°C.

A compound of the formula (I) or (II) wherein R^1 or R^{10} is chloro may also be prepared from a compound of the formula (III), by reacting the latter compound with lithium chloride and crown ether, in a suitable organic solvent such as THF, in a temperature range of ambient temperature to reflux. A compound of the formula (I) or (II) wherein R^1 or R^{10} is (1-4C)alkylthio or (1-4C)alkoxy may be prepared by reacting the compound of the formula (III) with sodium thio(1-4C)alkoxide or sodium (1-4C)alkoxide respectively, in an alcohol or THF, in a temperature range of 0°C to reflux.

Compounds of the formulae (IV) and (V) are conveniently reacted together in the presence of a strong base such as butyl lithium, lithium bistrimethylsilylamide, sodium hydride, lithium tert-butoxide or lithium diisopropylamide. The reaction is conveniently carried out in an inert solvent such as tetrahydrofuran (THF), dimethylformamide (DMF), N,N'-dimethylpropyleneurea (DMPU) or N-methylpyrrolidone in a temperature range of -78°C to -50°C for the deprotonation and cyclisation. Suitable values for R^{13} include ethyl and benzyl and suitable values for R^{14} include ethyl and n-propyl, preferably n-propyl.

A compound of the formula (IV) is conveniently prepared by reacting a chloroformate of the formula ($ClCOOR^{13}$) with a compound of the formula (IVA):

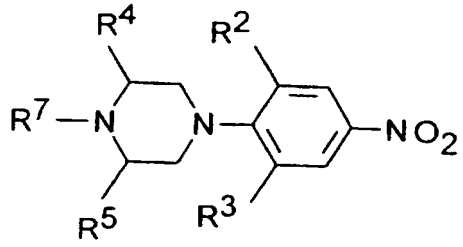


(IVA)

wherein R^2 - R^5 and R^7 are as hereinabove defined. The reaction is conveniently carried out in the presence of an inorganic or organic base such as sodium bicarbonate or an amine base

such as dimethylaniline. the former in a solvent such as acetone/water and the latter in an organic solvent such as THF. toluene. DMF or acetonitrile.

A compound of the formula (IVA) may be prepared by reducing a compound of the formula (IVB):

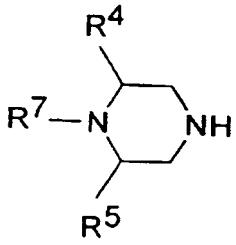


(IVB)

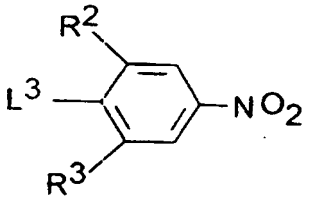
wherein R^2 - R^5 and R^7 are as hereinabove defined.

Many reduction methods suitable for the reduction of a nitro to an amino group are known in the art. for example catalytic hydrogenation. metal reductions or with reducing agents such as sodium hydrosulfite. Suitable catalysts in catalytic hydrogenation include Raney nickel. platinum metal and its oxide. rhodium. palladium-on-charcoal and Wilkinson's catalyst $RhCl(Ph_3P)_3$. Catalyst hydrogenation is conveniently carried out in the temperature range 0°C - 150°C. but preferably at ambient temperature at slightly above atmospheric pressure.

A compound of the formula (IVB) is conveniently prepared by reacting together compounds of the formulae (X) and (IVC):



(X)



(IVC)

wherein R^2 - R^5 and R^7 are as hereinabove defined and L^3 is a leaving group. preferably halo and in particular fluoro.

The reaction between compounds of the formulae (X) and (IVC) is carried out in the presence of an organic or inorganic base such as sodium bicarbonate, potassium carbonate or an amine base such as diisopropylethylamine, in an inert solvent such as acetonitrile, DMF, DMPU or N-methylpyrrolidone, in a temperature range of 50°C - 150°C.

Compounds of the formula (X) are conveniently prepared by reacting the appropriate piperazine ring with a compound of the formula (VII) using similar conditions to those described (see later) for the reaction between compounds of the formulae (VI) and (VII). It may be advantageous to protect one of the ring nitrogen atoms in the piperazine ring prior to the reaction with a compound of the formula (VII) and remove the protecting group thereafter. For compounds of the formula VII in which L^1 is not activated for displacement, more vigorous reaction conditions may be necessary, for example the Buchwald reaction using a strong base (such as potassium tert-butoxide or lithium bistrimethylsilylamide) and a catalyst (such as Pd(0)), as illustrated in Example 15. It is within the ordinary skill of an organic chemist to recognise when such reaction conditions are necessary.

Alternatively, a compound of the formula (IVB) may be formed by reacting the appropriate piperazine ring in which one of the ring nitrogen atoms is protected (with for example a (1-4C)alkoxycarbonyl group) with a compound of the formula (IVC). The ring nitrogen-protecting group may then be removed and R^7 introduced onto the ring nitrogen by reacting the product of the deprotection with a compound of the formula (VII).

Compounds of the formula (VII) may be prepared by introducing substituents into or modifying substituents in a known optionally substituted heteroaryl ring. Such conversions are well known to the skilled chemist, for example a cyano group may be hydrolysed to a carboxy group which in turn may be converted to a carbamoyl or alkoxycarbonyl group or reduced to a hydroxymethyl group; an amino group may be acylated to an alkanoylamino group; a thio group may be alkylated to an alkylthio group which in turn may be oxidised to an alkylsulfinyl or alkylsulfonyl group and a hydroxyalkyl group may be alkylated to an alkoxyalkyl group.

The reaction between compounds of the formulae (VI) and (VII) is conveniently carried out in the presence of a base, in an aprotic polar solvent; preferably one with a high boiling point, such as acetonitrile or dimethylformamide. Suitable bases include amine bases

such as triethylamine. The reaction is preferably carried out in the temperature range 50°C - 150°C. Suitable leaving groups for this reaction include halo, (1-4C)alkylthio, (1-4C)alkanesulfinyl, (1-4C)alkanesulfonyl or phenoxy. Preferably the leaving group is fluoro, chloro or (1-4C)alkanesulfonyl such as methanesulfonyl.

A compound of the formula (II) wherein R^{10} is of the formula $-N(CO_2R^{15})CO(1\text{-}4C)alkyl$ is conveniently prepared by reacting a compound of the formula (I) and (II) wherein R^1 or R^{10} is hydroxy with an amide of the formula $HN(CO_2R^{15})CO(1\text{-}4C)alkyl$ under Mitsunobu conditions. For example, in the presence of tri-n-butylphosphine and 1,1'-(azodicarbonyl)dipiperidine in an organic solvent such as THF, and in the temperature range 0°C - 60°C, but preferably at ambient temperature. Details of analogous Mitsunobu reactions are contained in Tsunoda et al. Tet. Letts., 34, 1639, (1993). Amides of the formula $HN(CO_2R^{15})CO(1\text{-}4C)alkyl$ may be prepared by standard procedures of organic chemistry which are within the ordinary skill of an organic chemist.

The group $-C(=O)R^b$ may be introduced into a compound of the formula (VIII) to give the appropriate compound of the formula (I) or (II) wherein R^1 or R^{10} is of the formula $-N(Me)C(=O)R^b$ using similar methods to those described for the introduction of the appropriate $-C(=O)R^a$ group into the compound of the formula (I) or (II) wherein R^1 or R^{10} is amino.

The compound of the formula (VIII) may be prepared by reacting a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino with formaldehyde and sodium borohydride or sodium cyanoborohydride, in an alcholic solvent such as ethanol or isopropanol, in a temperature range of 0°C to ambient temperature.

Suitable N-oxides of compounds of the formula (I) or (II) may be prepared directly from a corresponding parent compound of the formula (I) or (II) using techniques well known to the ordinary skilled organic chemist, such as, for example, using a peracid (such as m-chloroperbenzoic acid) or perphthalic acid in a suitable solvent (such as dioxan or a mixture of water and THF) at a suitable temperature (such as ambient temperature). Example 36 also illustrates possible suitable reagents and conditions for preparing suitable N-oxides. The preparation of suitable N-oxides by assembly from suitable N-oxide starting materials and the

use of the processes described in this specification is within the skill of the ordinary skilled organic chemist, and is illustrated by, for example, Example 18.

It is also possible to convert one R^7 group into another R^7 group as a final step in the preparation of a compound of the formula (I) or (II) (see the specific examples).

When an optically active form of a compound of the formula (I) is required, it may be obtained by carrying out one of the above procedures using an optically active starting material, or by resolution of a racemic form of the compound or intermediate using a standard procedure.

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof, for use as a medicament; and the use of a compound of the formula (I) of the present invention, or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the formula (I) or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof for the therapeutic treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester thereof and a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered with one or more known drugs selected from other clinically useful antibacterial agents (for example ß-lactams or aminoglycosides). These may include penicillins, for example oxacillin or flucloxacillin and carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness against methicillin-resistant staphylococci. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein product (BPI) or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100mg and 1g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of the compound of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

Antibacterial Activity

The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive

organisms. which are used to screen for activity against pathogenic bacteria. Notably. the pharmaceutically-acceptable compounds of the present invention show activity against enterococci. pneumococci and methicillin resistant strains of S. aureus and coagulase negative staphylococci. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The antibacterial properties of the compounds of the invention may also be demonstrated in-vivo in conventional tests. No overt toxicity or other untoward effects are observed when compounds of the formula I are so tested at conventional daily dose levels.

The following results were obtained on a standard in-vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot.

Staphylococci were tested on agar. using an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood. an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms.

Organism		MIC (µg/ml) Example 1
Staphylococcus aureus:		
	Oxford	0.5
	Novb. Res	1.0
	MRQR	1.0
Coagulase Negative Staphylococci		
	MS	0.25
	MR	0.5
Streptococcus pyogenes		
	C203	1.0

Enterococcus faecalis	1.0
Bacillus subtilis	0.25

Novb. Res = Novobiocin resistant

MRQR = methicillin resistant quinolone resistant

MR = methicillin resistant

MS = methicillin sensitive

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration:

(ii) operations were carried out at ambient temperature, that is in the range 18-26°C and in air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated:

(iv) yields are given for illustration only and are not necessarily the maximum attainable:

(v) the structure of end-products of the formula I were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were determined in DMSO-D6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz: chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; t, triplet, m, multiplet: fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected]:

(vi) intermediates were not generally fully characterised and purity was in general assessed by thin layer chromatographic, infra-red (IR), mass spectral (MS) or NMR analysis: and

(vii) in which :-

®	is a Trademark
DMF	is N,N-dimethylformamide
DMA	is N,N-dimethylacetamide
TLC	is thin layer chromatography
DMSO	is dimethylsulfoxide
$CDCl_3$	is deuterated chloroform
MS	is mass spectroscopy
ESP	is electrospray
THF	is tetrahydrofuran
TFA	is trifluoroacetic acid
NMP	is N-methylpyrrolidone
dba	is dibenzylideneacetone
DMPU	is N,N-dimethylpropyleneurea.

Example 1 : N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide 1.5 trifluoroacetate salt (500 mg, 1 mM) was dissolved in ethanol (20 ml). 2-Chloropyrimidine (125 mg, 1.1 mM) was added, followed by triethylamine (0.36 ml, 2.6 mM) and water (2 ml, to aid solubility), and the solution stirred at ambient temperature for 24 hours. Further 2-chloropyrimidine (62 mg, 0.5 mM) was added, and the mixture refluxed for 16 hours. The solution was evporated to dryness, water (20 ml) added to the residue, and the pH adjusted to 12 with 1N sodium hydroxide solution. The solution was extracted with ethyl acetate (2 x 20 ml), and the combined organic layers dried over magnesium sulfate, and evaporated. The white residue was chromatographed on silica, eluting with a gradient increasing in polarity from 0 to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (270 mg).

MS (ESP): 415 (MH^+)

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.03 (t, 4H); 3.40 (t, 2H); 3.70 (dd, 1H); 3.87 (t, 4H); 4.08 (t, 1H); 4.69 (m, 1H); 6.65 (t, 1H); 7.09 (t, 1H); 7.17 (dd, 1H); 7.49 (dd, 1H); 8.19 (t, 1H); 8.38 (d, 2H).

The N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide 1.5 trifluoroacetate salt starting material was prepared as follows :-

N-[(5S)-3-(3-Fluoro-4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (PCT patent application WO 93/23384 Example 1 (j), 1 g, 2.3 mM) was dissolved in dichloromethane (50 ml) under argon, and cooled in an ice-bath. TFA (12.7 ml) was added, and the mixture stirred at 0°C for 30 minutes. Solvent was evaporated, and the residue treated four times by evaporation with 30 ml portions of ethyl acetate to remove TFA. The required starting material as a remaining solid analysed for 1.5 moles of residual TFA.

MS (ESP): 337 (MH^+).

NMR (DMSO-D6 + CD_3COOD) δ: ~1.8 (obscured by solvent); 3.21 (t, 4H); 3.28 (t, 4H); 3.45 (t, 2H); 3.74 (dd, 1H); 4.19 (t, 1H); 4.73 (m, 1H); 7.12 (t, 1H); 7.21 (dd, 1H); 7.52 (dd, 1H).

Example 2 : N-[(5S)-3-(3-Fluoro-4-(4-(5-chloropyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (6.73 g, 15 mM) was dissolved in DMA (100 ml). Triethylamine (4.37 ml, 31.4 mM) was added, and the whole mixture stirred at ambient temperature under argon for 10 minutes. 2,5-Dichloropyrimidine (2.23 g, 15 mM) was added, and the solution heated to 100°C for 8 hours. After cooling, solvent was evaporated, and the residue slurried with water for 1 hour. Solid was filtered, washed with water (2 x 100 ml) and dried. The residue was chromatographed twice on silica by dry flash chromatography, eluting with a gradient increasing in polarity from 0 to 4% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (3.04 g).

Microanalysis: Found: C, 53.4; H, 4.8; N, 18.6%.

Required for $C_{20}H_{22}ClFN_6O_3$: C, 53.6; H, 4.9; N, 18.7%.

MS (ESP): 449 (MH^+) for $C_{20}H_{22}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.02 (t, 4H); 3.39 (t, 2H); 3.69 (dd, 1H); 3.86 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 7.08 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.19 (t, 1H); 8.43 (s, 2H).

The N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt starting material was prepared as follows :-

N-[(5S)-3-(3-Fluoro-4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (PCT patent application WO 93/23384, 34 g, 78 mM) was dissolved in dichloromethane (500 ml), and cooled in an ice-bath. TFA (50 ml) was added, and the mixture stirred at 0°C for 1.5 hours. Solvent was evaporated, and the residual oil dissolved in ethyl acetate (40 ml). Diethyl ether was added to turbidity (~75 ml), and the solution left to crystallise. Filtration gave product as the mono trifluroacetate salt (32.5 g).

Microanalysis: Found : C, 47.5; H, 5.0; N, 11.8

$C_{18}H_{22}F_4N_4O_5$ requires : C, 48.0; H, 4.9; N, 12.4

Example 3 : N-[(5S)-3-(3-Fluoro-4-(4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (90 mg, 0.2 mM) was dissolved in DMA (3 ml). Triethylamine (58 µL, 0.42 mM) was stirred in, then 2-chloro-4,6-dimethylpyrimidine (28.5 mg, 0.2 mM) was added, and the solution heated under argon at 160°C for 5 hours. After cooling, solvent was evaporated, and the residue chromatographed on a 5 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 3% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (50 mg).

MS (ESP): 443 (MH^+) for $C_{22}H_{27}FN_6O_3$

NMR ($CDCl_3$) δ: 2.03 (s, 3H); 2.31 (s, 6H); 3.09 (t, 4H); 3.60-3.71 (m, 2H); 3.75 (dd, 1H); 3.99 (t, 4H); 4.02 (t, 1H); 4.76 (m, 1H); 6.09 (brt, 1H); 6.29 (s, 1H); 6.95 (t, 1H); 7.08 (dd, 1H); 7.44 (dd, 1H).

Example 4 : N-[(5S)-3-(3-Fluoro-4-(4-(3,5-dichloropyridazin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) was dissolved in DMA (15 ml). Triethylamine (306 µL, 2.2 mM) was stirred in, then 3,4,5-trichloropyridazine (184mg, 1 mM) was added, and the solution heated to 100°C for 16 hours. After cooling, the mixture was diluted with water (50 ml) and extracted weith ethyl acetate (2 x 25 ml). The combined extracts were dried over magnesium sulfate, evaporated, and the residue chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (280 mg).

MS (ESP): 483 (MH^+) for $C_{20}H_{21}Cl_2FN_6O_3$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.13 (t, 4H); 3.39 (t, 2H); 3.57 (t, 4H); 3.69 (dd, 1H); 4.06 (t, 1H); 4.70 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.49 (dd, 1H); 8.21 (brt, 1H); 9.01 (s, 1H).

Example 5 : N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (0.9 g, 2 mM) was dissolved in NMP (25 ml), triethylamine (0.28 ml, 2 mM) and 3,6-dichloropyridazine (298 mg, 2 mM) were added, and the solution heated to 110°C for 24 hours. After cooling, solvent was evaporated, and the residue chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 4% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (165 mg).

MS (ESP): 449 (MH^+) for $C_{20}H_{22}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.83 (s, 3H); 3.06 (t, 4H); 3.39 (t, part obscured, 2H); 3.73 (t + m, 5H); 4.07 (t, 1H); 4.68 (m, 1H); 7.09 (t, 1H); 7.17 (dd, 1H); 7.42 (d, 1H); 7.48 (dd, 1H); 7.54 (d, 1H); 8.21 (t, 1H).

Example 6 : N-[(5S)-3-(3-Fluoro-4-(4-(pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (247 mg, 0.55 mM) was dissolved in ethanol (25 ml), and treated with triethylamine (77 µL, 0.55 mM). Palladium catalyst (10% on charcoal, 100 mg) was added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated, and the residue chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 2.5% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (79 mg).

MS (ESP): 415 (MH^+) for $C_{20}H_{23}FN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.06 (t, 4H); 3.38 (t, 2H); 3.70 (br, 5H); 4.06 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.16 (dd, 1H); 7.29 (d, 1H); 7.38 (dd, 1H); 7.49 (dd, 1H); 8.18 (brt, 1H); 8.55 (d, 1H).

Example 7 : N-[(5S)-3-(3-Fluoro-4-(4-(6-carbamoylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (225mg, 0.5 mM) was dissolved in DMA (15 ml), triethylamine (101 mg, 1 mM) was added, and the whole mixture stirred at ambient temperature under argon for 15 minutes. 3-Chloropyridazine-6-carboxamide (Heterocycles, 1992, 34, 225; 79 mg, 0.5 mM) was added, and the solution heated to 120°C for 6 hours. After cooling, solvent was evaporated, the residue dissolved in dichloromethane, and washed with saturated sodium bicarbonate solution. The organic layer was dried (magnesium sulfate) and evaporated, and the residue chromatographed on silica, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (150 mg).

MS (ESP): 458 (MH^+) for $C_{21}H_{24}FN_7O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.08 (t, 4H); 3.37 (t, 2H); 3.69 (dd, 1H); 3.86 (t, 4H); 4.07 (t, 1H); 4.69 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.39 (d, 1H); 7.50 (dd, 1H); 7.53 (brs, 1H); 7.86 (d, 1H); 8.14 (brs, 1H); 8.21 (brt, 1H).

Example 8 : N-[(5S)-3-(3-Fluoro-4-(4-(6-*n*-butyloxycarbonylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Using the method and scale of Example 7, but replacing the 3-chloropyridazine-6-carboxamide

with n-butyl 3-chloropyridazine-6-carboxylate (PCT patent application WO 96/03380; 108 mg, 0.5 mM), the title product (162 mg) was obtained after chromatography as in Example 7.

MS (ESP): 515 (MH^+) for $C_{25}H_{31}FN_6O_5$

NMR (DMSO-D6) δ: 0.92 (t, 3H); 1.40 (hextet, 2H); 1.68 (quintet, 2H); 1.81 (s, 3H); 3.09 (t, 4H); 3.38 (t, 2H); 3.69 (dd, 1H); 3.89 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.20 (dd, 1H); 7.33 (d, 1H); 7.50 (dd, 1H); 7.82 (d, 1H); 8.20 (brt, 1H).

Example 9 : N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(3-chloropyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 25, 0.67 g, 1.5 mM) was dissolved in a mixture of ethanol (100 ml) and DMF (50 ml), and treated with triethylamine (208 µL, 1.5 mM). Palladium catalyst (10% on charcoal, 100 mg) was added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated, and the residue azeotroped dry with toluene (100 ml). The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (235 mg).

MS (ESP): 415 (MH^+) for $C_{20}H_{23}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.06 (t, 4H); 3.39 (t, 2H); 3.71 (t + m, 5H); 4.07 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.49 (dd, 1H); 7.85 (d, 1H); 8.10 (t, 1H); 8.20 (brt, 1H); 8.39 (d, 1H).

Examples 10-14

Examples 10-14 were all prepared using the following procedure :-

Triethylamine (2 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) in DMA (20 ml) under argon. The resultant mixture was stirred at room temperature for 15 minutes, and the appropriate halo-heterocycle (1 mM) added. The mixture was heated with stirring at 110°C for 6 hours. After cooling the solvent was removed by centrifugal evaporation. The residue was mixed with water and the solid filtered. The crude solids were dissolved or slurried in dichloromethane and purified by silica Mega Bond Elut® chromatography, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. The relevant fractions were combined and the solvent evaporated to give the following compounds :-

Example 10 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methylaminocarbonylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 472 (MH^+) for $C_{22}H_{26}FN_7O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.79 (d, 3H); 3.08 (t, 4H); 3.38 (t, 2H); 3.69 (dd, 1H); 3.84 (t, 4H); 4.06 (t, 1H); 4.69 (m, 1H); 7.09 (t, 1H); 7.18 (dd, 1H); 7.38 (d, 1H); 7.50 (dd, 1H); 7.85 (d, 1H); 8.19 (brt, 1H); 8.77 (brq, 1H).

The appropriate halo-heterocycle, 3-chloro-6-methylaminocarbonylpyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (429 mg, 2 mM) was dissolved in ethanol (10 ml), and a solution of methylamine in ethanol (2M, 4 ml) added. The mixture was stirred at ambient temperature for 1 hour, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 3% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (304 mg).

NMR (DMSO-D6) δ: 2.81 (d, 3H); 8.06 (d, 1H); 8.20 (d, 1H); 9.17 (brs, 1H).

Example 11 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(2-methoxyethylaminocarbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 516 (MH^+) for $C_{24}H_{30}FN_7O_5$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.09 (t, 4H); 3.26 (s, 3H); 3.39 (t, 2H); 3.47 (m, 4H); 3.69 (dd, 1H); 3.88 (t, 4H); 4.08 (t, 1H); 4.69 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.40 (d, 1H); 7.50 (dd, 1H); 7.86 (d, 1H); 8.20 (brt, 1H); 8.70 (brs, 1H).

The appropriate halo-heterocycle, 3-chloro-6-(2-methoxyethylaminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (429 mg, 2 mM) was dissolved in ethanol (10 ml), and 2-methoxyethylamine (150 mg, 2 mM) added. The mixture was stirred at ambient temperature for 48 hours, and solvent then removed. The residue was chromatographed on a

10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (76 mg).

MS (ESP): 216 (MH^+) for $C_8H_{10}ClN_3O_2$

NMR (DMSO-D6) δ: 3.26 (s, 3H); 3.49 (m, 4H); 8.08 (d, 1H); 8.21 (d, 1H); 9.14 (brs, 1H).

Example 12 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(2-hydroxyethylaminocarbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 502 (MH^+) for $C_{23}H_{28}FN_7O_5$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.08 (t, 4H); 3.37 (m, 4H); 3.51 (q, 2H); 3.69 (dd, 1H); 3.85 (t, 4H); 4.07 (t, 1H); 4.67 (m, 1H); 4.74 (t, 1H); 7.09 (t, 1H); 7.18 (dd, 1H); 7.40 (d, 1H); 7.49 (dd, 1H); 7.86 (d, 1H); 8.20 (t, 1H); 8.67 (t, 1H).

The appropriate halo-heterocycle, 3-chloro-6-(2-hydroxyethylaminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and 2-hydroxyethylamine (488 mg, 8 mM) added. The mixture was stirred at ambient temperature for 48 hours, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (637 mg).

MS (ESP): 202 (MH^+) for $C_7H_8ClN_3O_2$

NMR (DMSO-D6) δ: 3.39 (q, 2H); 3.55 (q, 2H); 4.75 (t, 1H); 8.08 (d, 1H); 8.21 (d, 1H); 9.08 (brt, 1H).

Example 13 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(*bis*-(2-hydroxyethyl)aminocarbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 546 (MH^+) for $C_{25}H_{32}FN_7O_6$

^{1}H NMR (DMSO - D6): 1.83 (s, 3H); 3.08 (t, 4H); 3.40 (t, 2H); 3.49 (t, 2H); 3.55 (overlapping, 8H); 3.69 (dd, 1H); 3.81 (t, 3H); 4.08 (t, 1H); 4.69 (m, 1H); 4.78 (t, 1H); 7.12 (t, 1H); 7.19 (t, 1H); 7.38 (d, 1H); 7.51 (dd, 1H); 7.55 (t, 1H); 8.19 (t, 1H).

The appropriate halo-heterocycle, 3-chloro-6-(*bis*-(2-hydroxyethyl)aminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and bis-(2-hydroxyethyl)amine (488 mg, 8 mM) added. The mixture was stirred at ambient temperature for 48 hours, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (637 mg).

MS (ESP): 202 (MH^+) for $C_7H_8ClN_3O_2$

NMR (DMSO-D6) δ: 3.39 (q, 2H); 3.55 (q, 2H); 4.75 (t, 1H); 8.08 (d, 1H); 8.21 (d, 1H); 9.08 (brt, 1H).

Example 14 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methoxycarbonylmethylaminocarbonyl)-pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 530 (MH^+) for $C_{24}H_{28}FN_7O_6$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.10 (t, 4H); 3.37 (t, 2H); 3.63 (s, 3H); 3.69 (dd, 1H); 3.87 (t, 4H); 4.03 (d, 2H); 4.07 (t, 1H); 4.68 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.40 (d, 1H); 7.50 (dd, 1H); 7.86 (d, 1H); 8.20 (t, 1H); 9.13 (t, 1H).

The appropriate haloheterocycle, 3-chloro-6-methoxycarbonylmethylaminocarbonyl-pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and glycine methyl ester hydrochloride (1 g, 8 mM), and triethylamine (808 mg, 8 mM) added. The mixture was stirred at ambient temperature for 18 hours, and solvent removed. The residue was chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a

gradient increasing in polarity from 0 to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (85 mg). NMR (DMSO-D6) δ: 3.65 (s, 3H); 4.08 (d, 2H); 8.13 (d, 1H); 8.23 (d, 1H); 9.58 (brt, 1H).

Example 15 : N-[(5S)-3-(3-Fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

(5R)-5-Azidomethyl-3-(3-fluoro-4-(4-pyrimid-5-ylpiperazin-1-yl)phenyl)oxazolidin-2-one (430 mg, 1.08 mM) was dissolved in DMF (25 ml) and the solution purged with argon. Palladium (10% on carbon, 50 mg) was added, followed by acetic anhydride (240 µL, 2.16 mM) and the mixture hydrogenated at ambient temperature under hydrogen confined in a balloon for 6 hours. The mixture was filtered through celite, evaporated to dryness, and the residue chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (340 mg).

MS (ESP): 415 (MH^+) for $C_{20}H_{23}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.08 (t, 4H); 3.39 (m, 6H); 3.68 (dd, 1H); 4.07 (t, 1H); 4.69 (m, 1H); 7.10 (t, 1H); 7.18 (dd, 1H); 7.49 (dd, 1H); 8.20 (t, 1H); 8.53 (s, 2H); 8.61 (s, 1H).

The (5R)-5-azidomethyl-3-(3-fluoro-4-(4-pyrid-2-ylpiperazin-1-yl)phenyl)oxazolidin-2-one used as starting material was prepared as follows :-

Tris(dba)dipalladium (1.0 g, 1.09 mM) was added to a degassed, stirred solution of 5-bromopyrimidine (12.19 g, 77 mM), *N*-benzylpiperazine (40.5 g, 0.23 M), and tri-*o*-tolylphosphine (1.29 g, 4.24 mM) in toluene (500 ml) under argon. A solution of lithium bis(trimethylsilylamide) (1M in THF, 230 ml) was added dropwise with stirring at ambient temperature. The mixture was then heated with stirring at 100°C for 5 hours. After cooling, the mixture was partitioned between dilute hydrochloric acid (2N, 500ml) and diethyl ether (500 ml). The aqueous phase was separated, made basic with aqueous sodium hydroxide, and extracted with diethyl ether (3 x 500 ml). The combined organic extracts were washed with brine (250 ml), dried over magnesium sulfate, filtered and evaporated to dryness. The residue

was chromatographed on silica by dry flash chromatography, eluting with a gradient increasing in polarity from 0 to 2.5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give 1-benzyl-4-(pyrimid-5-yl)piperazine as an oil (5.15 g), which the NMR spectrum showed to be contaminated with 1-benzyl-4-(pyrimid-2-yl)piperazine. The mixture was used without further purification.

MS (ESP): 254 (MH^+) for $C_{15}H_{18}N_4$

NMR (DMSO-D6) δ: 2.62 (t, 4H); 3.35 (t, 4H); 7.32 (m, 5H); 8.34 (s, 2H); 8.68 (s, 1H).

Crude 1-benzyl-4-(pyrimid-5-yl)piperazine (5.3 g, 20 mM) and ammonium formate (5.26 g, 0.08 M) were dissolved in a mixture of methanol (100 ml) and water (0.5 ml), and treated with palladium (10% on carbon, 1.3 g) under argon. The mixture was heated to reflux for 3 hours, cooled, filtered through celite, and evaporated to dryness. The residue was treated with aqueous sodium carbonate (2M, 50 ml), and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried (magnesium sulfate) and evaporated, to give an oil containing 1-(pyrimid-5-yl)piperazine, mixed with 1-(pyrimid-2-yl)piperazine (3.35 g). The mixture was used as such in the next stage.

MS (ESP): 165 (MH^+) for $C_8H_{12}N_4$

3,4-Difluoronitrobenzene (1.53 ml, 1.38 mM) was dissolved in acetonitrile (60 ml), N,N-diisopropylethylamine (6.93 ml, 40 mM), and the above mixture of piperazines (2.72 g, 16.6 mM) added, and the mixture heated to reflux for 18 hours. Solvent was evaporated, and the residue rougly purified by chromatography on silica by dry flash chromatography, eluting with dichloromethane. Relevant fractions were combined and evaporated. This residue was split into three equal portions (500 mg) which were further purified by chromatography on a 90 g Biotage Kiloprep® silica column, eluting with 2.5% methanol in dichloromethane. Relevant fractions were combined to give 3-fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)nitrobenzene (1.2 g).

MS (ESP): 304 (MH^+) for $C_{14}H_{14}FN_5O_2$

NMR (DMSO-D6) δ: 3.43 (s, 8H); 7.23 (t, 1H); 8.02 (m, 2H); 8.53 (s, 2H); 8.61 (s, 1H).

3-Fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)nitrobenzene (2.08 g, 6.8 mM) was dissolved in a mixture of ethyl acetate (300 ml) and DMF (20 ml), and the solution flushed with argon. Palladium (10% on carbon, 125 mg) was added, and the mixture hydrogenated at ambient temperature and pressure to greater than the theoretical uptake of gas. The mixture was filtered through celite, washed with water (2 x 150 ml), then brine (100 ml), dried (magnesium sulfate) and evaporated to dryness, to give 5-amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluoro-benzene as a solid (1.7 g), which was used as such in the next stage.

MS (ESP): 274 (MH^+) for $C_{14}H_{16}FN_5$

NMR (DMSO-D6) δ: 2.96 (t, 4H); 3.36 (t, 4H); 4.98 (s, 2H); 6.31 (dd, 1H); 6.36 (dd, 1H); 6.80 (t, 1H); 8.50 (s, 2H); 8.58 (s, 1H).

5-Amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluorobenzene (1.7 g, 6.2 mM) was dissolved in dry dichloromethane (40 ml) under argon, and cooled to -4°C. Pyridine (0.63 ml, 7.79 mM) was added, followed by benzyl chloroformate (0.98 ml, 6.85 mM). The mixture was stirred for 72 hours at ambient temperature. The resulting suspension was diluted with 5% methanol in dichloromethane (100 ml), washed with water (2 x 50 ml), dried (magnesium sulfate), and evaporated to dryness. The residue was chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 2.5% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give 5-benzyloxycarbonyl-amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluorobenzene (1.31 g).

MS (ESP): 408 (MH^+) for $C_{22}H_{22}FN_5O_2$

NMR (DMSO-D6) δ: 3.34 (m, 8H); 5.13 (s, 2H); 7.01 (t, 1H); 7.16 (d, 1H); 7.35 (complex, 6H); 8.52 (s, 2H); 8.59 (s, 1H); 9.92 (s, 1H).

tert-Butanol (0.354 g, 3.19 mM) and dry THF (25 ml) were stirred under argon, and cooled to -10°C. n-Butyl lithium (1.6 M in *iso*hexane, 2.39 ml, 3.83 mM) was added dropwise, the mixture was stirred 10 minutes, then cooled to -70°C. A solution of 5-benzyloxycarbonyl-amino-2-(4-(pyrimid-5-yl)piperazin-1-yl)fluorobenzene (1.3 g, 3.19 mM) dissolved in dry DMPU (20 ml) was added dropwise. After stirring for 10 minutes, a solution of (R)-glycidyl-butyrate (0.55 g, 3.83 mM) in dry THF (10 ml) was added, and stirring continued at -78°C for 30 minutes. The temperature was allowed to rise to ambient over 16 hours, the mixture

treated with methanol (10 ml), and stirred for 10 minutes. The reaction was diluted with saturated aqueous sodium bicarbonate (20 ml) and extracted with ethyl acetate (3 x 25 ml). The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated. The residue, still containing DMPU, was chromatographed on a 20 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give (5R)-3-(4-(4-(pyrimid-5-yl)piperazin-1-yl)-3-fluorophenyl)-5-hydroxymethyloxazolidin-2-one (0.70 g).

MS (ESP): 374 (MH^+) for $C_{18}H_{20}FN_5O_3$

NMR (DMSO-D6) δ: 3.10 (m, 4H); 3.40 (m, 4H); 3.53 (m, 1H); 3.65 (m, 1H); 3.77 (t, 1H); 4.03 (t, 1H); 4.66 (m, 1H); 5.19 (t, 1H); 7.10 (t, 1H); 7.21 (d, 1H); 7.54 (d, 1H); 8.21 (s, 2H); 8.60 (s, 1H).

(5R)-3-(4-(4-(pyrimid-5-yl)piperazin-1-yl)-3-fluorophenyl)-5-hydroxymethyloxazolidin-2-one (0.654 g, 1.75 mM) was dissolved in pyridine (15 ml), and cooled under argon to 0°C. Triethylamine (0.292 ml, 2.1 mM) and methanesulfonyl chloride (0.163 ml, 2.1 mM) were added, and stirring continued at 0°C for 10 minutes, before allowing the temperature to reach ambient over 2 hours. Solvent was evaporated, and the residue dissolved in dichloromethane (50 ml). The solution was washed with water (3 x 40 ml), brine (25 ml), dried (magnesium sulfate) and evaporated. The solid residue was triturated with diethyl ether (20 ml), and (5R)-3-(3-fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)-5-(methanesulfonyloxymethyl)-oxazolidin-2-one filtered off (0.65 g).

MS (ESP): 452 (MH^+) for $C_{19}H_{22}FN_5O_5S$

NMR (DMSO-D6) δ: 3.13 (m, 4H); 3.23 (s, 3H); 3.42 (m, 4H); 3.80 (dd, 1H); 4.16 (t, 1H); 4.47 (m, 2H); 4.98 (m, 1H); 7.14 (t, 1H); 7.22 (dd, 1H); 7.50 (dd, 1H); 8.54 (s, 2H); 8.61 (s, 1H).

(5R)-3-(3-Fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)-5-(methanesulfonyloxymethyl)-oxazolidin-2-one (0.6 g, 1.33 mM) was dissolved in dry DMF (15 ml), sodium azide (520 mg, 8 mM) was added, and the mixture was heated at 80°C under argon for 7 hours. Solvent was evaporated, and the residue partitioned between ethyl acetate (50 ml) and water (50 ml). The organic layer was separated, reextracted with ethyl acetate (2 x 25 ml), dried (magnesium

sulfate) and evaporated. to give (5R)-5-azidomethyl-3-(3-fluoro-4-(4-(pyrimid-5-yl)piperazin-1-yl)phenyl)oxazolidin-2-one as a solid (0.46 g).

MS (ESP): 399 (MH^+) for $C_{18}H_{19}FN_8O_2$

NMR (DMSO-D6) δ: 3.12 (t, 4H); 3.41 (t, 4H); 3.66 (dd, 1H); 3.73 (complex, 2H); 4.11 (t, 1H); 4.86 (m, 1H); 7.11 (t, 1H); 7.21 (dd, 1H); 7.52 (dd, 1H); 8.53 (s, 2H); 8.61 (s, 1H).

Examples 16-26

Examples 16-26 (all of which are (5S) chiral compounds are summarised in Table 1 below) were prepared using the following procedure which employed a Zymark robotic system for multiple parallel synthesis :-

Triethylamine (2 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) in DMA (15 ml) under argon. The resultant mixture was stirred at room temperature for 10 minutes. This solution was then added to the appropriate halo-heterocycle (1 mM) and the mixture heated with stirring at 110°C for 6 hours. After cooling the solvent was removed by centrifugal evaporation (SAVANT AES2000) with radiant heating for 5 hours. The residue was mixed with water and the solid filtered. The purity at this stage was assessed by TLC. Impure materials were dissolved in a mixture of dichloromethane and methanol and purified by silica Mega Bond Elut® chromatography, using a suitable mixture of the two solvents, as determined from the TLC. The relevant fractions were combined and the solvent removed by centrifugal evaporation (SAVANT AES2000) on medium heat for 3 hours. Compounds so prepared were generally characterised by the presence of the correct molecular ion for MH^+ in their electrospray mass spectra, and by their HPLC retention time (in minutes), using the following system and elution parameters.

Column HYPERSIL ODS 5m

Flow rate 1.0 ml/min

Detector Wavelength 254l

Solvent A 1 mMol TFA/H_2O

Solvent B 1 mMol TFA/CH_3CN

Time	*% Solvent A*	*% Solvent B*
0	95	5
3	95	5
17	5	95
18	95	5
20	95	5

Table 1

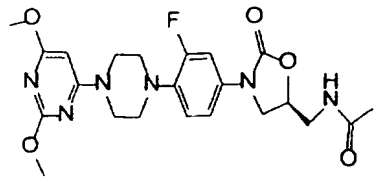
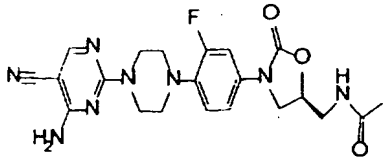
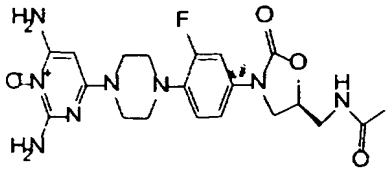
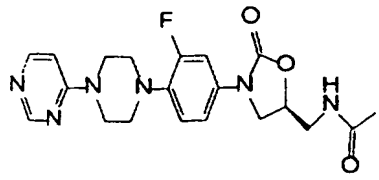
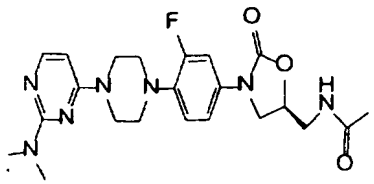
Example	Structure	Starting Material	HPLC RT	Mass ion	Notes
16	CHIRAL 	6-Chloro-2,4-dimethoxypyrimidine	17.6	475.2	2,3
17	CHIRAL 	4-Amino-2-chloro-5-cyanopyrimidine	16.9		2,4
18	CHIRAL 	2,6-Diamino-4-chloro-pyrimidine-1-oxide	15.3	461.4	1
19	CHIRAL 	4-Chloro-pyrimidine	14.7	415.3	1,7
20	CHIRAL 	4-Chloro-2-dimethylamino-pyrimidine	16.6	458.3	1

Table 1 continued

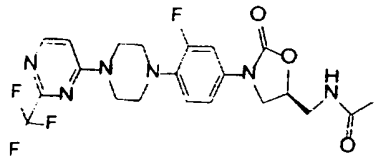
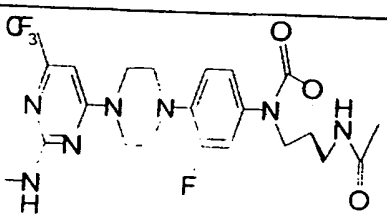
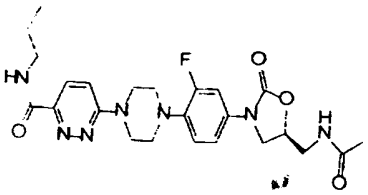
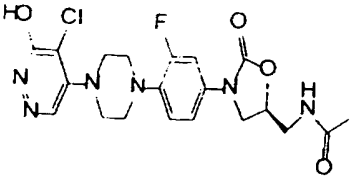
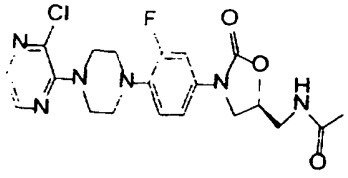
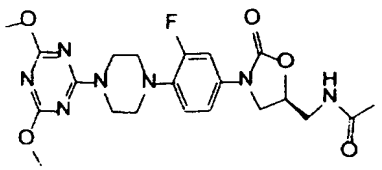
Example	Structure	Starting Material	HPLC RT	Mass ion	Notes
21	CHIRAL 	4-Chloro-2-trifluoromethyl-pyrimidine	20.8	483.2	1.8
22		2-Ethylamino-4-chloro-6-trifluoromethyl-pyrimidine	19.9	526.3	1.11
23	CHIRAL 	N-(n-Propyl)-3-chloro-pyridazine-6-carboxamide	17.7	500.3	1.9
24	CHIRAL 	4.5-Dichloro-3-hydroxy-pyridazine	16.5	465.2	1.10
25	CHIRAL 	2.3-Dichloropyrazine	20.3	449.2	1.5

Table 1 continued

Example	Structure	Starting Material	HPLC RT	Mass ion	Notes
26	CHIRAL 	2-Chloro-4,6-dimethoxy-1,3,5-triazine			2,6

Notes

1. Further purified by chromatography on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity in the range from 0% to 10% methanol in dichloromethane.

2. Obtained pure directly from reaction.

3. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(2,4-dimethoxypyrimid-6-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.00 (t, 4H); 3.37 (t, 2H); 3.51 (dd, 1H); 3.67 (t, 4H); 3.79 (2 x s, 6H); 4.06 (t, 1H); 4.68 (m, 1H); 5.77 (s, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.47 (dd, 1H); 8.21 (t, 1H).

4. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(4-amino-5-cyanopyrimid-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.00 (t, 4H); 3.39 (t, 2H); 3.69 (dd, 1H); 3.89 (t, 4H); 4.08 (t, 1H); 4.70 (m, 1H); 7.08 (t, 1H); 7.17 (dd, 1H); 7.29 (br, 2H); 7.49 (dd, 1H); 8.08 (d, 1H); 8.21 (t, 1H); 8.28 (s, 1H).

5. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(3-chloropyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.13 (t, 4H); 3.39 (t, 2H); 3.52 (t, 4H); 3.70 (dd, 1H); 3.89 (t, 4H); 4.08 (t, 1H); 4.70 (m, 1H); 7.08 (t, 1H); 7.17 (dd, 1H); 7.29 (br, 2H); 7.49 (dd, 1H); 8.08 (d, 1H); 8.21 (t, 1H); 8.28 (s, 1H).

6. Characterised by NMR

N-[(5S)-3-(3-Fluoro-4-(4-(4,6-dimethoxy-1,3,5-triazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 3.13 (t, 4H); 3.55-3.70 (m, 2H); 3.76 (dd, 1H); 3.97 (s, 6H); 4.02 (t + m, 5H); 4.77 (m, 1H); 6.10 (brt, 1H); 6.95 (t, 1H); 7.09 (dd, 1H); 7.46 (dd, 1H).

7. Preparation of starting material: J. Chem. Soc., 1951, 1218.

8. The appropriate haloheterocycle, 2-trifluoromethyl-4-chloropyrimidine, was prepared as follows :-

2-Trifluoromethyl-4-hydroxypyrimidine (1.06 g, 6.5 mM) was dissolved in thionyl chloride (10 ml) and DMF (10 drops) added. The mixture was heated to reflux for 1 hour, cooled, and solvent evaporated. The residue was partitioned between aqueous 2N potassium carbonate solution (50 ml) and dichloromethane (50 ml). The organic layer was separated, dried over sodium sulfate and evaporated to give the desired product, slightly contaminated with DMF (0.9 g).

NMR ($CDCl_3$) δ: 7.57 (d, 1H); 8.80 (d, 1H).

9. The appropriate haloheterocycle, N-(n-propyl)-3-chloropyridazine-6-carboxamide, was prepared as follows :-

Ethyl 3-chloropyridazine-6-carboxylate (Ref: Bull.Soc.Chim.France 1959, p 1793; 4.2 g, 22.6 mM) was dissolved in dry 1,2-dimethoxyethane (25 ml). n-propylamine (5 ml, 61 mM) added, and the mixture stirred at ambient temperature for 3 days. Solvent was removed, and the residue purified by dry column chromatography, using diethyl ether as eluant. Relevant

fractions were combined and evaporated, and the residue recrystallised from a mixture of diethyl ether and petrol. to give the desired product, mp 128.5°C-129.5°C (1.71 g).

Microanalysis: Found: C, 48.1; H, 5.4; N, 21.3; Cl, 18.1%

$C_8H_8ClNO_2$ requires: C, 48.1; H, 5.0; N, 21.1; Cl, 17.8%

10. Preparation of starting material: J. Amer. Chem. Soc., 1953, 75, 1909.

11. Characterised by NMR and MS

N-[(5S)-3-(3-Fluoro-4-(4-(2-ethylamino-6-trifluoromethylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 526 (MH^+) for $C_{23}H_{25}F_4N_7O_3$

NMR (DMSO-D6) δ: 1.07 (t, 3H); 1.81 (s, 3H); 3.00 (t, 4H); 3.23 (q, 2H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.77 (t, 4H); 4.06 (t, 1H); 4.65 (m, 1H); 6.42 (s, 1H); 7.07 (t, 1H); 7.10 (br, 1H); 7.17 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H).

Example 27 : N-[(5S)-3-(3-Fluoro-4-(4-(6-(*bis*(2-hydroxyethylamino)carbonyl)pyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Using the method and scale of Examples 10-14, the title product (248 mg) was obtained after chromatography.

MS (ESP): 546 (MH^+) for $C_{25}H_{32}FN_7O_6$

NMR (DMSO-D6) δ: 1.85 (s, 3H); 3.09 (t, 4H); 3.39 (t, 2H); 3.55 (m, 8H); 3.70 (dd, 1H); 3.83 (t, 4H); 4.08 (t, 1H); 4.68 (m, 1H); 4.77 (t, 2H); 7.12 (t, 1H); 7.18 (dd, 1H); 7.37 (d, 1H); 7.51 (dd, 1H); 7.55 (d, 1H); 8.19 (t, 1H).

The appropriate haloheterocycle, 3-chloro-6-(bis(2-hydroxyethyl)aminocarbonyl)pyridazine, was prepared as follows :-

n-Butyl 3-chloropyridazine-6-carboxylate (858 mg, 4 mM) was dissolved in ethanol (20 ml), and bis(2-hydroxyethyl)amine (841 mg, 8 mM) added. The mixture was stirred at ambient temperature for 24 hours, and solvent removed. The residue was chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient from 0% to 10% methanol in

dichloromethane. Relevant fractions were combined and evaporated to give the desired halo-heterocycle product (896 mg).

NMR (DMSO-D6) δ: 3.43 (s, 4H); 3.58 (q, 2H); 3.64 (q, 2H); 4.63 (t, 1H); 4.82 (t, 1H); 7.84 (d, 1H); 8.01 (d, 1H).

Example 28 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (0.9 g, 2 mM) was dissolved in DMA (10 ml), and triethylamine (0.556 ml, 4 mM) added. 3-Chloro-6-methylpyridazine (257 mg, 2 mM) was added and the mixture heated to 100°C for 18 hours. Solvent was evaporated, and the residue chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 1% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the desired product (61 mg), slightly contaminated with N-[(5S)-3-(3-fluoro-4-(4-formylpiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

MS (ESP): 429 (MH^+) for $C_{21}H_{25}N_6FO_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.42 (s, 3H); 3.06 (t, 4H); 3.37 (t, 2H); 3.66 (t overlapping m, 5H); 4.06 (t, 1H); 4.68 (m, 1H); 7.05 (t, 1H); 7.15 (dd, 1H); 7.23 (d, 1H); 7.29 (d, 1H); 7.48 (dd, 1H); 8.19 (t, 1H).

Example 29 : N-[(5S)-3-(3-Fluoro-4-(4-(4-chloro-6-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide and N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (1.35 g, 3 mM) was dissolved in DMA (30 ml), and triethylamine (606 mg, 6 mM) added under argon. 2,4-Dichloro-6-methylpyrimidine (489 mg, 3 mM) was added and the mixture heated to 110°C for 6 hours. Solvent was evaporated, and the residue dissolved in dichloromethane (100 ml). The solution was washed with water (50 ml), dried over magnesium sulfate and evaporated. The residue was purified by chromatography on a

90 g Biotage Kiloprep® silica column. Elution with 2.5% methanol in dichloromethane gave N-[(5S)-3-(3-fluoro-4-(4-(4-chloro-6-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (312 mg) - Example 29A.

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.27 (s, 3H); 2.99 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.83 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 6.65 (s, 1H); 7.08 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H).

Further elution with 5% methanol in dichloromethane gave N-[(5S)-3-(3-fluoro-4-(4-(2-chloro-6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (838 mg) - Example 29B.

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.80 (s, 3H); 2.23 (s, 3H); 3.00 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.72 (t, 4H); 4.05 (t, 1H); 4.68 (m, 1H); 6.76 (s, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.47 (dd, 1H); 8.18 (t, 1H).

Example 30 : N-[(5S)-3-(3-Fluoro-4-(4-(2-methyl-6-chloropyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (1.35 g, 3 mM) was dissolved in DMA (30 ml), and triethylamine (606 mg, 6 mM) added under argon. 4,6-Dichloro-2-methylpyrimidine (489 mg, 3 mM) was added and the mixture heated to 110° for 6 hours. Solvent was evaporated, and the residue dissolved in dichloromethane (100 ml). The solution was washed with water (50 ml), dried over magnesium sulfate and evaporated to give the desired product plus residual DMA.

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.34 (s, 3H); 2.99 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.76 (t, 4H); 4.05 (t, 1H); 4.67 (m, 1H); 6.79 (s, 1H); 7.06 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H).

Example 31 : N-[(5S)-3-(3-Fluoro-4-(4-(4-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(4-chloro-6-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 29A, 153 mg, 0.33 mM) was dissolved in a mixture of ethanol (40 ml) and DMF (10 ml). Triethylamine (92 µL, 0.66 mM) and palladium catalyst (10% on charcoal, 100 mg) were added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated. The residue was dissolved in dichloromethane (200 ml), washed with water, dried over magnesium sulfate and evaporated to give the title product (90 mg).

MS (ESP): 429 (MH^+) for $C_{21}H_{25}FN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.26 (s, 3H); 2.98 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.84 (t, 4H); 4.06 (t, 1H); 4.68 (m, 1H); 6.52 (d, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.48 (dd, 1H); 8.18 (t, 1H); 8.21 (d, 1H).

Example 32 : N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Using the same technique as Example 31, but starting with N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 29B, 692 mg, 1.5 mM) the title product was obtained (470mg).

MS (ESP): 429 (MH^+) for $C_{21}H_{25}FN_6O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 2.25 (s, 3H); 2.99 (t, 4H); 3.37 (t, 2H); 3.67 (dd, 1H); 3.73 (t, 4H); 4.05 (t, 1H); 4.68 (m, 1H); 6.73 (s, 1H); 7.07 (t, 1H); 7.16 (dd, 1H); 7.47 (dd, 1H); 8.18 (t, 1H); 8.37 (s, 1H).

Example 33 : N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Using the same technique as Example 31, but starting with N-[(5S)-3-(3-Fluoro-4-(4-(2-methyl-6-chloropyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 30, 1.34 g, 2.69 mM) the title product was obtained (690mg).

MS (ESP): 429 (MH^+) for $C_{21}H_{25}FN_6O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 2.36 (s, 3H); 3.00 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.72 (t, 4H); 4.07 (t, 1H); 4.68 (m, 1H); 6.66 (d, 1H); 7.08 (t, 1H); 7.17 (dd, 1H); 7.48 (dd, 1H); 8.08 (d, 1H); 8.19 (t, 1H).

Example 34 : N-[(5S)-3-(3-Fluoro-4-(4-(1,2,4-triazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Triethylamine (0.5 ml, 3.6 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (157 mg, 0.34 mM) in acetonitrile (5 ml), and 3-methylsulfinyl-1,2,4-triazine (50 mg, 0.34 mM) added. The resultant mixture was heated with stirring at 75°C for 18 hours. After cooling the solvent was evaporated, the residue dissolved in dichloromethane and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 5% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the title product (106 mg).

MS (ESP): 416 (MH^+) for $C_{19}H_{22}FN_7O_3$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.06 (t, 4H); 3.38 (t, 2H); 3.69 (t, 1H); 3.94 (t, 4H); 4.07 (t, 1H); 4.69 (m, 1H); 7.08 (t, 1H); 7.16 (dd, 1H); 7.50 (dd, 1H); 8.18 (t, 1H); 8.34 (d, 1H); 8.63 (d, 1H).

The 3-methylsulfinyl-1,2,4-triazine used as starting material was prepared as follows :-

3-Methylthio-1,2,4-triazine (J. Het. Chem., 1970, 7, 767; 254 mg, 2 mM) was dissolved in dichloromethane (5 ml) and stirred at ambient temperature. 3-Chloroperoxybenzoic acid (50% strength, 690 mg, 2 mM) was added in portions over 30 minutes. The mixture was washed with saturated aqueous sodium bicarbonate (5 ml), dried (magnesium sulfate), and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 0% to 10% methanol in dichloromethane. Relevant fractions were combined and evaporated to give 3-methylsulfinyl-1,2,4-triazine as a gum (60 mg).

MS (ESP): 144 (MH^+) for $C_4H_5N_3OS$

NMR (DMSO-D6) δ: 2.97 (s, 3H); 9.05 (d, 1H); 9.58 (d, 1H).

Example 35 : N-[(5S)-3-(3-Fluoro-4-(4-(1,3,5-triazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

Triethylamine (0.21 ml, 1.5 mM) was added to a stirred solution of N-[(5S)-3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide trifluoroacetate salt (450 mg, 1 mM) in 1,4-dioxane (20 ml), and 2-phenoxy -1,3,5-triazine (J. Amer. Chem. Soc., 1975, 97, 1851; 173 mg, 1 mM) added. The resultant mixture was heated to reflux for 4 hours. After cooling the solvent was evaporated, the residue dissolved in 5% methanol in dichloromethane and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 3% to 11% methanol in dichloromethane. Relevant fractions were combined and evaporated to give the product contaminated with phenol, which was rechromatographed as above eluting with a gradient increasing in polarity from 0% to 7% methanol in dichloromethane to give a pure sample (38 mg).

MS (ESP): 416 (MH^+) for $C_{19}H_{22}FN_7O_3$

NMR (DMSO-D6) δ: 1.81 (s, 3H); 3.02 (t, 4H); 3.37 (t, 2H); 3.68 (dd, 1H); 3.92 (t, 4H); 4.07 (t, 1H); 4.68 (m, 1H); 7.08 (t, 1H); 7.19 (dd, 1H); 7.50 (dd, 1H); 8.23 (t, 1H); 8.58 (s, 2H).

Example 36 : N-[(5S)-3-(3-Fluoro-4-(1-oxo-4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 1, 207 mg, 0.5 mM) was dissolved in a mixture of methanol (10 ml) and dichloromethane (5 ml), and magnesium monoperoxyphthalate.$6H_2O$ (90%, 279 mg, 0.51 mM) was added. After stirring for 4 hours, precipitated phthalic acid was filtered off, and solvents removed. Solvent was evaporated, the residue preabsorbd on silica, and chromatographed on a 10 g silica Mega Bond Elut® column, eluting with a gradient increasing in polarity from 5% to 20% methanol in dichloromethane. Relevant fractions were combined and evaporated to give title product (38 mg) slightly contaminated with phthalic acid.

MS (ESP): 431 (MH+) for $C_{20}H_{23}FN_6O_4$

NMR (DMSO-D6) δ: 1.82 (s, 3H); 3.05 (d, 2H); 3.39 (t, 2H); 3.75 (dd, 1H); 3.92 (quintet, 4H); 4.13 (t, 1H); 4.62 (d, 2H); 4.74 (m, 1H); 6.72 (t, 1H); 7.42 (dd, 1H); 7.64 (dd, 1H); 8.22 (t, 1H); 8.42 (d, 2H); 8.63 (t, 1H).

Example 37 : N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide and N-[(5S)-3-(3-Fluoro-4-(4-(4-chloro-5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide

N-[(5S)-3-(3-Fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide trifluoroacetate salt (900 mg, 2 mM) was dissolved in DMA (20 ml), and triethylamine (610 mg, 6 mM) added. 2,4-Dichloro-5-methylpyrimidine (326 mg, 2 mM) was added and the mixture heated to 100°C for 18 hours. Solvent was evaporated, and the residue partitioned between dichloromethane (40 ml) and water (20 ml). The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by dry column chromatography on silica eluting with a gradient increasing in polarity from 0% to 7% methanol in dichloromethane. The minor, less polar component (13 mg) was N-[(5S)-3-(3-fluoro-4-(4-(4-chloro-5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 37A).

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 2.17 (s, 3H); 3.09 (t, 4H); 3.56-3.71 (m, 2H); 3.75 (dd, 1H); 3.93 (t, 4H); 4.03 (t, 1H); 4.76 (m, 1H); 6.04 (t, 1H); 6.94 (t, 1H); 7.08 (dd, 1H); 7.46 (dd, 1H); 8.10 (s, 1H).

The major, more polar component (400 mg) was N-[(5S)-3-(3-fluoro-4-(4-(2-chloro-5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 37B).

MS (ESP): 463 (MH^+) for $C_{21}H_{24}ClFN_6O_3$

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 2.24 (s, 3H); 3.14 (t, 4H); 3.57-3.69 (m, 2H); 3.74 (t overlapping m, 5H); 4.03 (t, 1H); 4.78 (m, 1H); 6.24 (t, 1H); 6.94 (t, 1H); 7.08 (dd, 1H); 7.45 (dd, 1H); 7.97 (s, 1H).

Example 38 : N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide

N-[(5S)-3-(3-Fluoro-4-(4-(2-chloro-5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide (Example 37B; 380 mg, 0.82 mM) was dissolved in methanol (30 ml), and treated with triethylamine (230 µL, 1.7 mM). Palladium catalyst (10% on charcoal, 40 mg) was added, and the mixture hydrogenated under balloon pressure for 18 hours. Catalyst was filtered off through celite, solvent evaporated, and the residue partitioned between dichloromethane (20 ml) and water (10 ml). The organic layer was dried over magnesium sulfate and evaporated to give the title product (290 mg).

MS (ESP): 429.4 (MH^+) for $C_{21}H_{25}FN_6O_3$

NMR ($CDCl_3$) δ: 2.03 (s, 3H); 2.26 (s, 3H); 3.17 (t, 4H); 3.63 (t overlapping m, 6H); 3.76 (dd, 1H); 4.03 (t, 1H); 4.77 (m, 1H); 6.29 (t, 1H); 6.96 (t, 1H); 7.09 (dd, 1H); 7.45 (dd, 1H); 8.16 (s, 1H); 8.63 (s, 1H).

Example 39

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a) Tablet I

	mg/tablet
Compound X	100
Lactose Ph.Eur	179
Croscarmellose sodium	12
Polyvinylpyrrolidone	6
Magnesium stearate	3

(b) Tablet II

	mg/tablet
Compound X	50
Lactose Ph.Eur	229
Croscarmellose sodium	12
Polyvinylpyrrolidone	6
Magnesium stearate	3

(c)	Tablet III	mg/tablet
	Compound X	1
	Lactose Ph.Eur	92
	Croscarmellose sodium	4
	Polyvinylpyrrolidone	2
	Magnesium stearate	1

(d)	Capsule	mg/capsule
	Compound X	10
	Lactose Ph.Eur	389
	Croscarmellose sodium	100
	Magnesium stearate	1

(e)	Injection I	(50 mg/ml)
	Compound X	5.0% w/v
	Isotonic aqueous solution	to 100%

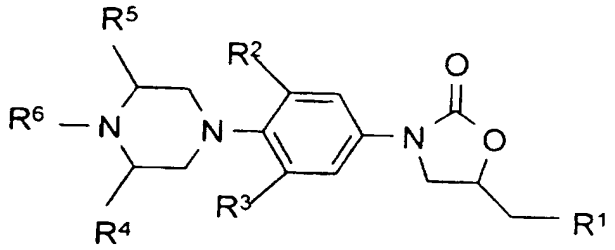
Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS

1. A compound of the formula (I)



(I)

wherein:

R^1 is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, (1-4C)alkylthio, (1-4C)alkylaminocarbonyloxy, or of the formula $-NHC(=O)R^a$ wherein R^a is hydrogen, (1-4C)alkoxy, amino, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl, methylamino, dimethylamino or (1-4C)alkyl or R^1 is of the formula $-N(Me)C(=O)R^b$ wherein R^b is hydrogen, methyl or methoxy or R^1 is of the formula $-NHS(O)_n$(1-4C)alkyl wherein n is 0, 1 or 2;

R^2 and R^3 are independently hydrogen or fluoro;

R^4 and R^5 are independently hydrogen or methyl;

R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl (optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino), halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylS(O)$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl (optionally substituted by carboxy or (1-4C)alkoxycarbonyl), (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; suitable N-oxides thereof and in-vivo-hydrolysable esters thereof.

2. A compound of the formula (I), as claimed in claim 1, wherein:

R^1 is hydroxy, chloro, fluoro, (1-4C)alkanesulfonyloxy, amino, azido, (1-4C)alkoxy, or R^1 is of the formula $-NHC(=O)R^a$ wherein R^a is hydrogen, (1-4C)alkoxy, chloromethyl, dichloromethyl, cyanomethyl, methoxymethyl, acetylmethyl or (1-4C)alkyl or R^1 is of the formula $-NHSO_2$(1-4C)alkyl;

R^2 and R^3 are independently hydrogen or fluoro;

R^4 and R^5 are independently hydrogen or methyl;

R^6 is a 6-membered heteroaryl ring containing 2 or 3 ring nitrogen atoms as the only ring heteroatoms, linked via a ring carbon atom and optionally substituted on a ring carbon atom by one, two or three substituents independently selected from (1-4C)alkyl [optionally substituted by trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkoxy, carboxy, hydroxy, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl, cyano, nitro, amino, N-(1-4C)alkylamino, di-(N-(1-4C)alkyl)amino or (2-4C)alkanoylamino], halo, trifluoromethyl, (1-4C)alkylS(O)$_n$- (wherein n is 0, 1 or 2), (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino, carboxy, hydroxy, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, di-(N-(1-4C)alkyl)carbamoyl [wherein the (1-4C)alkyl group or groups in the last two-mentioned carbamoyl substituents is optionally substituted by hydroxy, (1-4C)alkoxy or (1-4C)alkoxycarbonyl], (2-4C)alkenyl [optionally substituted by carboxy or (1-4C)alkoxycarbonyl], (1-4C)alkoxy, cyano or nitro;

pharmaceutically-acceptable salts thereof; suitable N-oxides thereof and in-vivo-hydrolysable esters thereof.

3. A compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1 and 2, except that the following optional substituents on R^6, namely (1-4C)alkoxy, (1-4C)alkylSO$_2$amino, (1-4C)alkanoylamino and those N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl substituents with the (1-4C)alkyl group or groups substituted by hydroxy, (1-4C)alkoxy or

(1-4C)alkoxycarbonyl, are excluded; and the number of optional substituents on R^6 is restricted to one or two.

4. A compound of the formula (I), or a pharmaceutically-acceptable salt or suitable N-oxide thereof as claimed in claims 1-3, wherein : R^1 is acetamido, one of R^2 and R^3 is hydrogen and the other is fluoro, R^4 and R^5 are both hydrogen, R^6 is pyrimidine or pyrazine and the optional substituents on the heteroaryl ring are independently selected from methyl, chloro, nitro, cyano, carbamoyl, N-(1-4C)alkylcarbamoyl and di-(N-(1-4C)alkyl)carbamoyl.

5. A compound of the formula (I), as claimed in claims 1-3, selected from N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-nitropyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(4-amino-5-cyanopyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(4-methylpyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(2-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl-methyl]acetamide:

N-[(5S)-3-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

N-[(5S)-3-(4-(4-(pyrimidin-4-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

N-[(5S)-3-(4-(4-(pyrimidin-5-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

and pharmaceutically-acceptable salts and suitable N-oxides thereof.

6. A compound of the formula (I), as claimed in claims 1-3, selected from

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(3-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(5-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3,5-Difluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide;

N-[(5S)-3-(3-Fluoro-4-(4-(6-methylpyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

N-[(5S)-3-(3-Fluoro-4-(4-(6-chloropyridazin-3-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide:

and pharmaceutically-acceptable salts, and suitable N-oxides, thereof.

7. A compound of the formula (I), or a pharmaceutically-acceptable salt or suitable

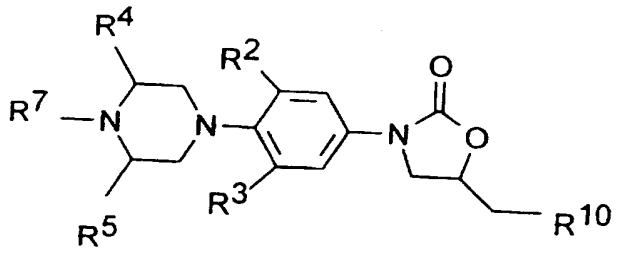
N-oxide thereof, as claimed in claims 1-3, selected from

N-[(5S)-3-(3-Fluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]acetamide: and

N-[(5S)-3-(3-Fluoro-4-(4-(pyrazin-2-yl)piperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl]-acetamide.

8. A process for the preparation of a compound of the formula (I), as claimed in claim 1, which comprises :-

(a) the deprotection of a compound, containing at least one protecting group, of the formula (II), a pharmaceutically-acceptable salt , suitable N-oxide or in-vivo hydrolysable ester thereof :

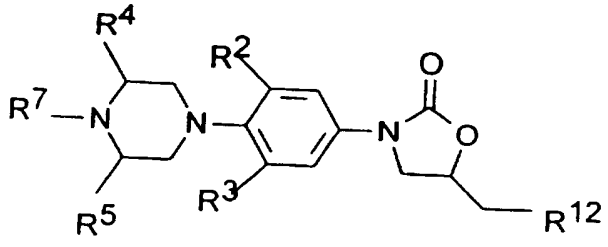


(II)

(b) the modification of a substituent in or the introduction of a substituent into another compound of formula (I) or (II);

(c) when R^1 or R^{10} is of the formula - $NHS(O)_n$(1-4C)alkyl, wherein n is 1 or 2, the oxidation of a compound of the formula (I) wherein n is 0 or, when n is 2 the oxidation of a compound of the formula (I) or (II) wherein n is 1;

(d) when R^1 or R^{10} is azido, the reaction of a compound of the formula (III) with a source of azide:



(III)

(e) when R^1 or R^{10} is amino, the reduction of a compound of the formula (I) or (II) wherein R^1 or R^{10} is azido;

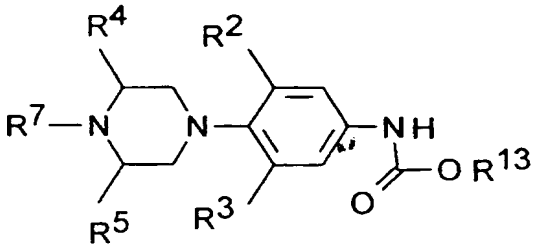
(f) when R^1 or R^{10} is of the formula $-NHC(=O)R^a$, the introduction of $-C(=O)R^a$ into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

(g) when R^1 or R^{10} is of the formula $-NHS(O)_n$ (1-4C)alkyl the introduction of $-S(O)_n$ (1-4C)alkyl into a compound of the formula (I) or (II) wherein R^1 or R^{10} is amino;

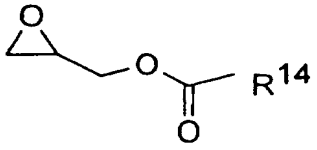
(h) when R^1 or R^{10} is chloro, fluoro, (1-4C)alkanesulfonyloxy or (1-4C)alkylaminocarbonyloxy, from a compound of the formula (I) or (II) wherein R^1 or R^{10} is hydroxy;

(i) when R^1 or R^{10} is chloro, (1-4C)alkylthio or (1-4C)alkoxy, from a compound of the formula (III);

(j) when R^1 or R^{10} is hydroxy, the reaction of a compound of the formula (IV) with a compound of the formula (V):

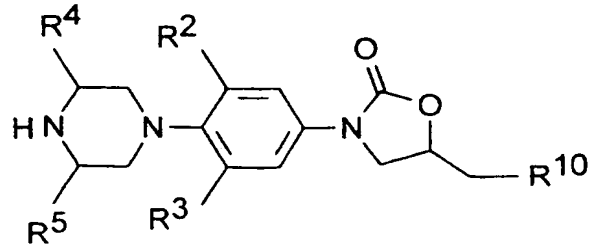


(IV)



(V)

(k) the reaction of a compound of the formula (VI) with a compound of the formula (VII):



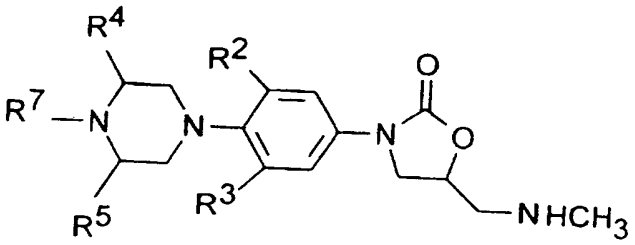
R^7-L^1

(VI)

(VII)

(l) when R^{10} is of the formula -N(CO_2R^{15})CO(1-4C)alkyl: from a compound of the formula (I) and (II) wherein R^1 or R^{10} is hydroxy;

(m) when R^1 or R^{10} is of the formula -N(Me)C(=O)R^b, by the introduction of the group -C(=O)R^b into a compound of the formula (VIII):



(VIII)

and

(n) when a suitable N-oxide is required, by preparation directly from a corresponding parent compound of the formula (I) or (II), or by assembly from suitable N-oxide starting materials:

wherein R^2, R^3, R^4 and R^5 are as hereinabove defined, R^7 is R^6 or protected R^6, R^{10} is R^1 or protected R^1, R^{12} is mesyloxy or tosyloxy, R^{13} is (1-6C)alkyl or benzyl, R^{14} is (1-6C)alkyl, R^{15} is (1-4C)alkyl or benzyl and L^1 is a leaving goup and thereafter if necessary:

i) removing any protecting groups;

ii) forming a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo hydrolysable ester;

and when an optically active form of a compound of the formula (I) is required it may be obtained by carrying out one of the above procedures using an optically active starting material, or by resolution of a racemic form of the compound or intermediate using a standard procedure.

9. A pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1-7 and a pharmaceutically-acceptable diluent or carrier.

10. A method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1-7.

11. The use of a compound of the formula (I), or a pharmaceutically-acceptable salt, suitable N-oxide or in-vivo-hydrolysable ester thereof, as claimed in claims 1-7, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/GB 97/01767

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/12 A61K31/495 A61K31/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 23384 A (THE UPJOHN COMPANY) 25 November 1993 see claims	1-4,9-11
Y	WO 93 09103 A (THE UPJOHN COMPANY) 13 May 1993 see claims	1-4,9-11
Y	WO 95 14684 A (THE UPJOHN COMPANY) 1 June 1995 see claims	1-4,9-11
P,X	WO 97 21708 A (PHARMACIA & UPJOHN COMPANY) 19 June 1997 see the whole document	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establis the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 1997	26.09.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/01767

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 10
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/GB 97/01767

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